Ceftolozane/Tazobactam Activity Against Gram-negative Bacteria Causing Urinary Tract Infections in European Hospitals (2011-2012): A Report From an International Antimicrobial Surveillance Program

Sandra McCurdy[1], Peter J Petersen[1], Judith Steenbergen[1], David J Farrell[2], Matteo Bassetti[3]

[1]Cubist, Lexington, MA, USA; [2]JMI Laboratories, North Liberty, IA, USA; [3]Infectious Diseases Division, Santa Maria Misericordia University Hospital, Udine, Italy

Sandra McCurdy , MS, M (ASCP)
Scientist
Clinical Microbiology
Cubist
65 Hayden Avenue
Lexington, MA, 02421, USA
Email: sandra.mccurdy@cubist.com

Poster #eP445

INTRODUCTION

- Urinary tract infections (UTIs) are usually caused by Gram-negative bacteria, with the majority of hospital-associated UTIs attributable to the pathogens *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas aeruginosa*.[1]
- Antimicrobial drug resistance due to the presence of multidrug-resistant (MDR) and extended-spectrum β-lactamase (ESBL)–producing strains of bacteria is a common feature of cUTIs, and is increasing[2]; the investigation of new antimicrobial treatments is therefore warranted.
- Ceftolozane/tazobactam (TOL/TAZ), a novel antibacterial consisting of ceftolozane, an antipseudomonal cephalosporin, with tazobactam, a well-established β-lactamase inhibitor, has been investigated in 2 Phase 3 clinical trials for the treatment of patients with complicated UTI.[3]
- In this study, the aim was to evaluate the activity of TOL/TAZ and comparator agents against a collection of clinically isolated Gram-negative organisms obtained from European patients with UTI, as part of the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS).

METHODS

- A total of 1727 nonduplicate bacterial isolates were collected from patients with UTI attending 31 hospitals in 15 countries: Belgium, France, Germany, Greece, Ireland, Israel, Italy, Poland, Portugal, Russia, Spain, Sweden, Turkey, UK, and Ukraine, during 2011-2012 and forwarded to a central laboratory (JMI Laboratories, North Liberty, IA, USA) for confirmatory identification and susceptibility testing.
- Antimicrobial susceptibility testing was carried out for TOL/TAZ and several comparators that are commonly used to treat UTI in Europe, including levofloxacin (LVX), piperacillin/tazobactam (PIP/TAZ), ceftazidime (CAZ), and meropenem (MEM).
- Minimum inhibitory concentration (MIC) values were determined using standard broth microdilution assays with dry-form Sensititre® panels (TREK Diagnostic Systems, Oakwood Village, OH, USA), according to Clinical Laboratory Standards Institute methodology.[4,5]
- ESBL phenotypes in *E. coli* and *Klebsiella pneumoniae* were defined as having an MIC ≥2 mg/L for ceftazidime or ceftriaxone or aztreonam.
- MDR phenotypes were defined as being nonsusceptible (NS) to ≥1 agent in ≥3 antimicrobial drug classes.
- Interpretations of susceptibility (S) for all antimicrobials except for TOL/TAZ were based on the European Committee on Antimicrobial Susceptibility Testing's criteria.[6]
- A proposed susceptible breakpoint of 8 mg/L was used for TOL/TAZ, which was tested at a fixed 4 mg/L concentration of TAZ.

RESULTS

- The most frequently isolated pathogens from patients with UTIs were *E. coli* (n = 950; 55%), *K. pneumoniae* (n = 192; 11.1%), and *P. aeruginosa* (n = 141; 8.2%). In *E. coli* and *K. pneumoniae*, 15.3% and 42.2% displayed an ESBL-positive phenotype, and 42.6% of *P. aeruginosa* isolates were classified as MDR.
- Of the 81 isolates of ESBL-positive *K. pneumoniae*, 13.6% were NS to MEM **(Table 1)**, suggesting the presence of the *K. pneumoniae* carbapenemase. This phenotype is still relatively rare, and was observed in 5.7% of *K. pneumoniae* UTI isolates in this European study.
- The MICs required to inhibit the growth of 50%/90% of organisms ($MIC_{50/90}$) for TOL/TAZ against *E. coli, K. pneumoniae,* and *P. aeruginosa* were 0.25/0.5, 0.5/32, and 0.5/32 mg/L, respectively. At an MIC of 8 mg/L, TOL/TAZ inhibited 100% of ESBL-producing *E. coli*, 69.1% of ESBL-producing *K. pneumoniae* **(Table 1)**, and 73.3% of MDR *P. aeruginosa* **(Figure 1)**. Against LVX NS (n = 260) and PIP/TAZ NS (n = 95) *E. coli*, TOL/TAZ inhibited 100% of isolates at a concentration of 8 mg/L **(Table 1)**.
- TOL/TAZ demonstrated greater activity than PIP/TAZ against all ESBL-positive isolates that were tested, including *E. coli* ($MIC_{50/90}$, 0.5/1 vs 8/64 mg/L), *K. pneumoniae* ($MIC_{50/90}$, 2/>32 vs 32/>64 mg/L), and MEM S *K. pneumoniae* (2/>32 vs 16/>64 mg/L) **(Table 2)**.
- Against *P. aeruginosa* isolates that were NS to multiple β-lactamases (n = 41), the $MIC_{50/90}$ for TOL/TAZ and PIP/TAZ was 4/>32 and >64/>64 mg/L, respectively **(Table 2)**.

RESULTS (cont'd)

Table 1. Summary of TOL/TAZ Activity Tested Against Drug-Resistant Isolates of *E. coli*, *K. pneumoniae*, and *P. aeruginosa* collected From Patients With UTI in Europe (2011-2012)

Organism or Group (No. Tested)	No. of Isolates (Cumulative %) Inhibited at MIC (mg/L) of:													
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
E. coli (950)	2 (0.2)	6 (0.8)	288 (31.2)	504 (84.2)	**110 (95.8)**	29 (98.8)	7 (99.6)	2 (99.8)	2 (100.0)				0.25	0.5
ESBL-phenotype (145)	0 (0.0)	0 (0.0)	3 (2.1)	36 (26.9)	69 (74.5)	**27 (93.1)**	6 (97.2)	2 (98.6)	2 (100.0)				0.5	1
LVX NS (>1 mg/L 260)	0 (0.0)	1 (0.4)	34 (13.5)	132 (64.2)	64 (88.9)	**20 (96.5)**	6 (98.9)	1 (99.2)	2 (100.0)				0.25	1
LVX R (>2 mg/L 258)	0 (0.0)	1 (0.4)	34 (13.6)	130 (64.0)	64 (88.8)	**20 (96.5)**	6 (98.8)	1 (99.2)	2 (100.0)				0.25	1
PIP/TAZ NS (95)	0 (0.0)	0 (0.0)	8 (8.4)	35 (45.3)	32 (79.0)	**15 (94.7)**	3 (97.9)	0 (97.9)	2 (100.0)				0.5	1
K. pneumoniae (192)	0 (0.0)	1 (0.5)	21 (10.9)	69 (47.4)	40 (68.2)	13 (75.0)	11 (80.7)	11 (86.5)	1 (87.0)	4 (89.1)	**5 (91.7)**	16 (100.0)	0.5	32
ESBL-phenotype (81)	0 (0.0)	0 (0.0)	1 (1.2)	9 (12.4)	15 (30.9)	9 (42.0)	10 (54.3)	11 (67.9)	1 (69.1)	4 (74.1)	5 (80.3)	**16 (100.0)**	2	>32
ESBL-phenotype MEM S (70)	0 (0.0)	0 (0.0)	1 (1.4)	9 (14.3)	15 (35.7)	9 (48.6)	10 (62.9)	11 (78.6)	1 (80.0)	2 (82.9)	3 (87.1)	**9 (100.0)**	2	>32
ESBL-phenotype MEM NS (11)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2%)	2 (36.4%)	**7 (100)**	>32	>32
P. aeruginosa (141)	0 (0.0)	0 (0.0)	1 (0.7)	5 (4.3)	74 (56.7)	26 (75.2)	12 (83.7)	4 (86.5)	3 (88.7)	0 (88.7)	**3 (90.8)**	13 (100.0)	0.5	32
MEM NS (37)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	7 (21.6)	4 (32.4)	6 (48.7)	2 (54.1)	2 (59.5)	0 (59.5)	3 (67.6)	**12 (100.0)**	4	>32
PIP/TAZ NS (57)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (19.3)	12 (40.4)	11 (59.7)	4 (66.7)	3 (79.1)	0 (71.9)	3 (71.9)	**13 (100.0)**	2	>32
LVX NS (54)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	14 (27.8)	12 (50.0)	7 (63.0)	2 (66.7)	2 (70.4)	0 (70.4)	3 (75.9)	**13 (100.0)**	1	>32
MDR (60)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (16.7)	15 (41.7)	12 (61.7)	4 (68.3)	3 (73.3)	0 (73.3)	3 (78.3)	**13 (100.0)**	2	>32

Bold text indicates MIC_{90}; underlined text indicates MIC_{50}.
R, resistant.

Table 2. In Vitro Activity of TOL/TAZ and Comparator Agents Tested Against Gram-negative Isolates Collected From Patients With UTI in Europe (2011-2012)

	Range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S[a]
E. coli (n = 950)				
TOL/TAZ	**0.03->8**	**0.25**	**0.5**	**100**
LVX	≤0.12->4	≤0.12	>4	72.6
PIP/TAZ	≤0.5->64	2	8	90.0
CAZ	0.03->32	0.12	4	86.1
MEM	≤0.06-0.25	≤0.06	≤0.06	100
E. coli ESBL phenotype (n = 145)				
TOL/TAZ	**0.12-8**	**0.5**	**1**	**100**
LVX	≤0.12->4	>4	>4	26.2
PIP/TAZ	≤0.5->64	8	64	63.4
CAZ	0.12->32	8	>32	9.0
MEM	≤0.06-0.25	≤0.06	≤0.06	100
E. coli LVX NS (n = 260)				
TOL/TAZ	**0.06-8**	**0.25**	**1**	**100**
LVX	NA	NA	NA	NA
PIP/TAZ	≤0.5->64	2	32	75.8
CAZ	0.06->32	0.25	32	61.5
MEM	≤0.06-≤0.06	≤0.06	≤0.06	100
K. pneumoniae (n = 192)				
TOL/TAZ	**0.06->32**	**0.5**	**32**	**87.0**
LVX	≤0.12->4	0.25	>4	67.2
PIP/TAZ	≤0.5->64	4	>64	67.2
CAZ	<0.06->32	0.5	>32	59.9
MEM	≤0.06->8	≤0.06	≤0.06	94.3
K. pneumoniae ESBL phenotype (n = 81)				
TOL/TAZ	**0.12->32**	**2**	**>32**	**69.1**
LVX	≤0.12->4	4	>4	37.0
PIP/TAZ	2->64	32	>64	35.8
CAZ	0.5->32	32	>32	4.9
MEM	≤0.06->8	≤0.06	>8	86.4
K. pneumoniae ESBL MEM NS (n = 11)				
TOL/TAZ	**16->32**	**>32**	**>32**	**0**
LVX	2->4	>4	>4	0
PIP/TAZ	>64->64	>64	>64	0
CAZ	>32->32	>32	>32	0
MEM	NA	NA	NA	NA
K. pneumoniae ESBL MEM S (n = 70)				
TOL/TAZ	**0.12->32**	**2**	**>32**	**80.0**
LVX	≤0.12->4	4	>4	42.9
PIP/TAZ	2->64	16	>64	41.4
CAZ	0.5->32	32	>32	5.8
MEM	NA	NA	NA	NA
P. aeruginosa (n = 141)				
TOL/TAZ	**0.12->32**	**0.5**	**32**	**88.7**
LVX	≤0.12->4	0.5	>4	61.7
PIP/TAZ	≤0.5->64	8	>64	59.6
CAZ	0.5->32	4	32	69.5
MEM	≤0.06->8	0.5	>8	73.8
P. aeruginosa MDR (n = 60)				
TOL/TAZ	**0.5->32**	**2**	**>32**	**73.3**
LVX	0.25->4	>4	>4	20.0
PIP/TAZ	4->64	64	>64	11.7
CAZ	0.5->32	16	>32	28.3
MEM	0.12->8	4	>8	43.3
P. aeruginosa CAZ NS (n =43)				
TOL/TAZ	**0.5->32**	**4**	**>32**	**62.8**
LVX	0.25->4	>4	>4	23.2
PIP/TAZ	16->64	>64	>64	7.0
CAZ	8->32	32	>32	NA
MEM	0.25->8	8	>8	32.6
P. aeruginosa FEP NS (n = 57)				
TOL/TAZ	**0.5->32**	**2**	**>32**	**71.9**
LVX	0.25->4	>4	>4	21.1
PIP/TAZ	4->64	64	>64	12.3
CAZ	0.5->32	16	>32	28.1
MEM	≤0.06->8	4	>8	43.9
P. aeruginosa GEN NS (n = 33)				
TOL/TAZ	**0.5->32**	**2**	**>32**	**57.5**
LVX	1->4	>4	>4	12.1
PIP/TAZ	8->64	64	>64	18.2
CAZ	0.5->32	16	>32	33.3
MEM	0.12->8	8	>8	36.4
P. aeruginosa MEM NS (n = 37)				
TOL/TAZ	**0.25->32**	**2**	**>32**	**59.5**
LVX	0.25->4	>4	>4	10.8
PIP/TAZ	4->64	64	>64	13.5
CAZ	1->32	32	>32	21.6
MEM	4->8	8	>8	0.0
P. aeruginosa PIP/TAZ NS (n = 57)				
TOL/TAZ	**0.5->32**	**2**	**>32**	**71.9**
LVX	0.25->4	>4	>4	26.3
PIP/TAZ	16->64	64	>64	0.0
CAZ	0.5->32	16	>32	24.6
MEM	0.25->8	4	>8	43.9
P. aeruginosa LVX NS (n = 54)				
TOL/TAZ	**0.25->32**	**1**	**>32**	**70.4**
LVX	2->4	>4	>4	0.0
PIP/TAZ	≤0.5->64	64	>64	22.2
CAZ	0.5->32	8	>32	38.9
MEM	0.12->8	4	>8	38.9
P. aeruginosa multiple BL-NS (n = 41)				
TOL/TAZ	**0.5->32**	**4**	**>32**	**61**
LVX	≤0.25->4	>4	>4	19.5
PIP/TAZ	16->64	>64	>64	0
CAZ	NA	NA	NA	NA
MEM	≤0.25->8	8	>8	29.3

BL, β-lactamase; FEP, cefepime.
[a]Susceptibility was determined by using a proposed breakpoint of 8 mg/L for TOL/TAZ.

Table 3. TOL/TAZ %S Against Enterobacteriaceae Isolates (N = 1560) Collected From Patients With UTI in Europe (2011-2012)

Country	No. of Isolates	MIC (mg/L) Range	50%	90%	%S[a]
Belgium	41	0.12-16	0.25	1	97.6
France	311	0.06->32	0.25	0.5	99.0
Germany	172	0.03->32	0.25	0.5	98.8
Greece	65	0.12->32	0.25	0.5	95.4
Ireland	135	0.12-32	0.25	1	97.7
Israel	22	0.12->32	0.25	2	90.9
Italy	94	0.12->32	0.25	2	95.7
Poland	22	0.12->32	32	>32	27.3
Portugal	87	0.06->32	0.25	2	95.4
Russia	18	0.12->32	0.5	16	83.3
Spain	228	0.12->32	0.25	0.5	99.6
Sweden	126	0.12-2	0.25	0.5	100
Turkey	111	0.12->32	0.25	1	98.2
UK	114	0.12-8	0.25	0.5	100
Ukraine	14	0.06-2	0.5	2	100

[a]Susceptibility was determined by using a proposed breakpoint of 8 mg/L for TOL/TAZ.

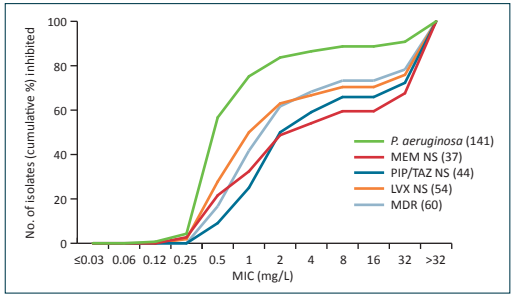
Table 4. TOL/TAZ %S Against *P. aeruginosa* Isolates (N = 141) Collected From Patients With UTI in Europe (2011-2012)

Country	No. of Isolates	MIC (mg/L) Range	50%	90%	%S[a]
Belgium	2	0.5->32	-	-	50
France	21	0.5-2	0.5	2	100
Germany	16	0.25-2	0.5	1	100
Greece	8	1->32	-	-	87.5
Ireland	8	0.25-1	-	-	100
Israel	-	-	-	-	-
Italy	15	0.5-2	0.5	2	100
Poland	3	>32	-	-	0
Portugal	23	0.5->32	4	>32	56.5
Spain	16	0.5-4	0.5	2	100
Sweden	7	0.5-1	-	-	100
Turkey	4	0.5->32	-	-	75
UK	18	0.12-1	0.5	1	100
Ukraine	-	-	-	-	-

[a]Susceptibility was determined by using a proposed breakpoint of 8 mg/L for TOL/TAZ.

- In all isolates of *E. coli, K. pneumoniae*, and *P. aeruginosa* that were tested, (wild-type and resistant phenotype subsets) TOL/TAZ demonstrated greater activity than CAZ, including a 16-fold higher MIC_{50} against ESBL-producing *E. coli* and ESBL-producing *K. pneumoniae*, and an 8-fold higher MIC_{50} against MDR *P. aeruginosa* **(Table 2)**.
- Small numbers of Enterobacteriaceae isolates with TOL/TAZ MICs >8 mg/L were found in Belgium (n = 1), France (n = 3), Germany (n = 2), Greece (n = 3), Ireland (n = 3), Israel (n = 2), Italy (n = 4), Portugal (n = 4), Russia (n = 3), Spain (n = 1), and Turkey (n = 2). Poland had the highest proportion of isolates (16/22 tested) with MICs >8 mg/L.
- In all countries except Russia and Poland, Enterobacteriaceae susceptibility to TOL/TAZ was >90%. In Sweden, the UK, and Ukraine, 100% of isolates were susceptible to TOL/TAZ **(Table 3)**.
- *P. aeruginosa* susceptibility to TOL/TAZ was 100% in France, Germany, Ireland, Italy, Spain, Sweden, and the UK **(Table 4)**.

Figure 1. Summary of TOL/TAZ Activity Against Resistant Isolates of *P. aeruginosa* Collected From Patients With UTI in Europe (2011-2012)



CONCLUSIONS

- TOL/TAZ demonstrated potent activity against Enterobacteriaceae and *P. aeruginosa* isolates that were collected from patients at 31 sites in 15 European countries. This activity was maintained against most ESBL-producing pathogens and in isolates that were NS to commonly used antibiotics.
- Lower susceptibility to TOL/TAZ by *P. aeruginosa* in Belgium, Poland, and Portugal might have been due to the presence of metallo-β-lactamase–producing isolates, which have been previously reported in Europe.[7]
- Against *P. aeruginosa*, including all drug-resistant strains, TOL/TAZ demonstrated superior in vitro activity to MEM, PIP/TAZ, LVX, and CAZ.
- These data support a role for TOL/TAZ in the treatment of patients with UTI in Europe.

ACKNOWLEDGEMENTS AND DISCLOSURES

Editorial support for this poster was provided by PAREXEL and funded by Cubist.

SM, PJP, and JS are employees of Cubist. MB is a consultant and speaker for Cubist.

REFERENCES

1. Tandogdu Z, et al. *World J Urol.* 2013 Aug 24 [Epub ahead of print].
2. Zilberberg MD, Shorr AF. *Infect Control Hosp Epidemiol.* 2013;34:940-946.
3. Wagenlehner F, et al. Presented at the 24th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), May 10-13, 2014, Barcelona, Spain. Poster eP449.
4. Clinical and Laboratory Standards Institute. 2012. *Performance standards for antimicrobial susceptibility testing: 24th informational supplement.* CLSI document M100-S24. CLSI, Wayne, PA.
5. Clinical and Laboratory Standards Institute. 2012. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved standard, 9th ed.* CLSI document M7-A9. CLSI, Wayne, PA.
6. European Committee on Antimicrobial Susceptibility Testing (2014). Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0, January 2014. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 1, 2014.
7. Castanheira M, et al. Presented at the 23rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); April 27-30, 2013; Berlin, Germany. Poster P1339.